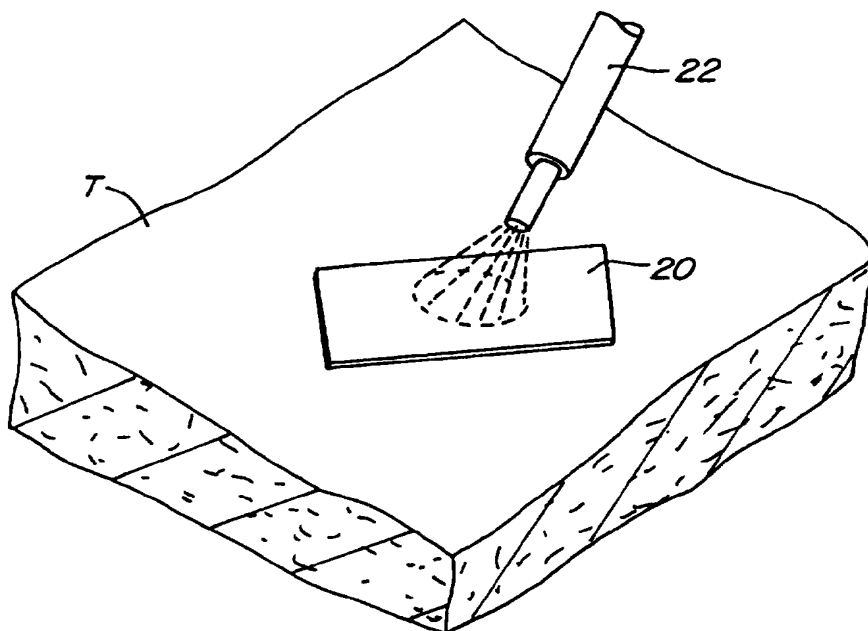


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(54) Title: METHODS AND ARTICLES FOR FUSING MATRIX LAYERS CONTAINING NON-COLLAGENOUS PROTEINS TO TISSUE			

**(57) Abstract**

A matrix material (12) containing a non-collagenous protein component is fused to tissue (T) by first placing the matrix material (12) over a target location (W) on the tissue (T) and then applying energy to the matrix material (12). The non-collagenous protein component is of a type wherein the energy is applied in an amount which together result in fusion of the matrix to the tissue.

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METHODS AND ARTICLES FOR FUSING MATRIX LAYERS CONTAINING NON-COLLAGENOUS PROTEINS TO TISSUE

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates generally to methods and articles for fusing matrix materials to form layers over tissue. More particularly, the present invention relates to fusing matrix layers containing non-collagenous proteins to tissues for wound closure, and other purposes.

The application and fusing of material layers to tissue is useful for a number of purposes. Of particular interest to the present invention, matrix materials may be applied to tissue in order to effect or enhance wound closure, to augment and repair tissue defects, and the like. A variety of specific compositions and methods have been devised for such purposes. For example, the fusing of collagen and other proteins by the application of laser and other energy sources has been suggested for the closure of wounds. See, for example, U.S. Patent Nos. 5,156,613; 5,209,776; and 5,071,417. The application of pre-polymer materials followed by light-induced cross-linking has also been proposed. See, for example, PCT publications WO 94/24962 and WO 94/21324.

While holding great promise, such methods and compositions for the placement of matrix materials on tissue could be improved in a number of respects. For example, it would be desirable to provide improved materials which fuse or adhere to the underlying tissue with an enhanced bonding strength upon the application of energy. It would also be desirable to provide materials having enhanced tensile strength, both before and after the application of energy. Such materials should also possess a degree of elasticity and conformability to enhance positioning and adherence to the underlying tissue, particularly when the tissue undergoes movement which can stress the matrix material. The materials should further meet the appropriate biocompatibility profile

and, least in some instances, biodegradable so that they can be resorbed or degraded over time. In addition, the materials should be compatible with the intended use (indication) and the underlying tissue type.

5 The subject matter of the present application is related to that of the following commonly owned copending applications: USSN 08/303,336 (published as WO 96/07355 on March 14, 1996); USSN 08/481,712 (published as WO 96/07356 on March 14, 1996); USSN 08/673,710, filed on June 19, 1996; USSN
10 60/011,898, filed on February 20, 1996; USSN 08/704,852 (Attorney Docket No. 17067-002000), filed on August 27, 1996; and USSN 60/_____ (Attorney Docket No. 17067-002100), filed on October 21, 1996. The full disclosures of each of these applications are incorporated herein by reference.

15 It would thus be desirable to provide methods and articles for fusing matrix layers to tissue which are improved in at least one or more of the aspects listed above.

SUMMARY OF THE INVENTION

20 The present invention provides improved methods and articles for fusing a matrix material to tissue for a variety of purposes, including wound closure, tissue augmentation, or the like. The matrix material comprises a non-collagenous protein component which when placed over a target location on
25 the tissue will fuse to the tissue upon the application of energy, such as radio frequency energy, laser energy, ultrasonic energy, heat, infrared, microwave or the like. The energy will be applied in an amount sufficient to fuse the matrix material to the underlying tissue with a peel bond
30 strength of at least about 0.03 N/cm. Thus, as used herein, the terms "fuse" and "fusing" will mean that the matrix material has been caused to adhere to the underlying tissue with a peel bond strength (defined below) of at least about 0.03 N/cm. Although the precise energy level will depend on
35 the nature of the protein, the nature of the energy source and the nature of the underlying tissue, typically it will be in the range from about 1 W/cm² to about 100 W/cm². Exemplary non-collagenous proteins include albumins, such as bovine

serum albumin (BSA), ovalbumin, human serum albumin (HSA); hemoglobins from human, bovine, and other sources; fibrinogens from human, bovine, and other sources; fibronectins from human, bovine, and other sources; elastins; keratins; laminins; and the like.

The matrix material may be applied (prior to exposure to energy) in a variety of forms, usually being a solid, mesh, or composite layer. Alternatively, the matrix material may comprise a dispersible, non-solid phase, such as liquids, gels, sols, suspensions, powders, and the like. In some cases, the matrix material may comprise substantially pure protein, but in many cases it will be desirable to combine additional components, such as carrier materials, reinforcement materials, plasticizers, and the like. After the application of energy, a layer of the matrix material will usually fuse to the underlying tissue with the requisite peel bond strength. The layer will typically have a thickness of at least about 0.01 mm, usually being in the range from about 0.05 mm to about 0.1 mm, and the layer will usually form a substantially continuous surface on the underlying tissue. The area may vary widely, typically being at least about 0.05 cm², usually being in the range from about 1 cm² to about 100 cm².

Articles according to the present invention comprise a sheet of the matrix material generally as described above. The sheets will usually be sterilized and present in a sterile package for distribution and storage prior to use.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a perspective view of a sheet of matrix material according to the present invention.

Fig. 2 is a top view of a package containing the matrix material of Fig. 1, shown with a portion broken away.

Fig. 3 is a schematic illustration of a region of tissue having a wound therein.

Fig. 4 illustrates the method of the present invention wherein a solid sheet of matrix material is placed

over the wound of Fig. 3 and radio frequency (RF) energy is used to fuse the matrix material to the tissue."

Fig. 5 illustrates an alternative embodiment of the method of the present invention, wherein a liquid or gel matrix material is applied using a syringe to the wound in the tissue of Fig. 3.

Fig. 6 illustrates the application of RF energy to the liquid matrix material of Fig. 5.

Fig. 7 illustrates a resulting layer of matrix material which has been bonded to tissue according to the method of the present invention.

DESCRIPTION OF THE SPECIFIC EMBODIMENTS

Methods and articles according to the present invention may be used for fusing matrix materials to tissue for a variety of purposes. Tissues include virtually all human and animal body tissues, including the skin (epidermis), as well as the external and internal surfaces of virtually all body organs. The present invention is particularly useful for fusing matrix materials to fragile body organs, such as lungs, stomach, liver, spleen, intestines, colon, fallopian tubes, esophagus, ovary, uterus, bladder, and the like. The matrix material may be applied for a variety of purposes, including wound closure, tissue augmentation, and the like. Wounds to be treated may result from accidental trauma, surgical intervention, or virtually any other cause. Tissue augmentation will usually be performed to fill or cover regions of tissue where tissue has been lost or damaged, such as abrasions, burns, and the like.

The matrix materials of the present invention will comprise a non-collagenous protein component, as described in more detail below. The non-collagenous protein will be selected to provide for bonding of the resulting layer of matrix material, typically providing a peel bond strength of at least about 0.03 N/cm, preferably at least about 0.07 N/cm, and usually in the range from about 0.07 N/cm to about 0.2 N/cm. Peel bond strength can be measured by conventional techniques. A particular method for measuring peel bond

strength is as follows. Pieces of the matrix material (1.5 cm x 3 cm) are cut and glued to a plastic tab (1.5 cm x 3 cm) which overlaps the test material by 1 cm over the width (the 1.5 cm dimension), using a cyanoacrylate glue. A hole is pierced in the tab, and the test material bonded to the tissue *in vivo* or *in vitro*. A digital force gauge, such as an Omega DFO51-2 fitted with a 2 pound force transducer, Omega Instruments, Stamford, Connecticut, is attached to the plastic tab using a hook attachment which is secured to hole in the plastic tab. A manual upward force is then applied on the force gauge, and the sample peeled off with an even rate of pull, typically about 3 cm per second. Peel strengths are recorded in force (Newtons) divided by the width of the sample (1.5 cm) in order to determine the peel bond strength. The peel bond strength is measured as a maximum.

The non-collagenous protein component may comprise one, two, or more individual proteins. Exemplary non-collagenous proteins include albumins, such as bovine serum albumin (BSA), ovalbumin, human serum albumin (HSA); hemoglobins from human, bovine, and other sources; fibrinogens from human, bovine, and other sources; fibronectins from human, bovine, and other sources; elastin; keratin; and laminin. The proteins may comprise substantially all of the matrix material, or may comprise only a portion thereof. In the latter case, additional components may be included, such as carrier substances, reinforcing materials (e.g., reinforcing meshes, fibers, filaments, braids and the like), and plasticizers. Exemplary carrier substances include collagen, gelatin, fibrinogen, and elastin.

The matrix material will usually be in the form of a solid layer, e.g., in the form of a sheet, film, patch, strip, mesh, or the like. The use of a mesh allows tissue to form a coagulum within the interstices of the mesh as energy is applied, as described in copending application serial no. 08/303,336, the disclosure of which is incorporated herein by reference. As mentioned above, the solid phase forms of the matrix material may optionally be reinforced with filaments, braids, meshes, and other woven and non-woven reinforcement

materials. Usually, the reinforcement materials will be non-bioabsorbable so that they will remain even after the fusible material has been resorbed. Exemplary reinforcement materials include polymeric braids or meshes, particularly composed of polypropylene (Marlex®), fluorinated hydrocarbon polymers (Gore-Tex®), polyesters (such as Dacron®), and the like. In other cases, the reinforcement materials may be biodegradable. Exemplary biodegradable materials include polylactic acid, polyglycolic acid, copolymers of lactic acid and glycolic acid, polyhydroxybutyrate, other poly (α -hydroxy acids) polydioxanone, and the like. Filaments, braids, meshes, woven and non-woven forms may be used.

Reinforced and non-reinforced matrix materials may be formed by conventional techniques for forming and solidifying proteins. Usually, the proteins will be cross-linked to enhance structural integrity. For example, the proteins may be dissolved in water to form a gel. The gel may then be layered over a flat surface to a desired thickness, and the gel dried to form a solid sheet. Such sheets will typically have a thickness in the range from about 0.03 mm to about 0.15 mm, usually from about 0.05 mm to about 0.1 mm. The sheets will preferably have an area of at least about 0.5 cm², preferably at least about 1 cm², and usually in the range from about 1 cm² to about 100 cm². It will be appreciated that sheets of various sizes can be trimmed to an appropriate size and shape for a particular application.

Alternatively, the matrix materials may be applied to the target region on the tissue in a non-solid dispersible state, e.g., as a liquid, gel, paste, spray, sol or combination thereof. Such dispersible matrix materials may be applied using syringes, brushes, sprayers, spatulas, or other methods suitable for spreading or dispersing a layer of the material over the wound region. Usually, the layer will have a thickness in the range from about 0.01 mm to about 5 mm, preferably from about 0.05 mm to about 1 mm.

The method of the present invention will utilize energy of a type and in an amount sufficient to fuse the matrix material including the non-collagenous protein to

underlying tissue. Suitable energy sources include electrical energy, particularly radio frequency (RF) energy, heat energy, laser energy, ultrasonic energy, infrared, microwave, and the like. Preferred are the use of RF energy sources, such as those available as electrosurgical power supplies from companies such as Valleylab, Boulder, Colorado, and Con-Med, Utica, New York, employing conventional RF-applying probes. Particularly preferred are modified RF energy sources which provide for a dispersed or distributed current flow from a hand-held probe to the tissue. One such RF energy source is referred to as a radio frequency inert gas device or inert gas beam coagulator which relies on flow of an inert ionizable gas, such as argon, for conducting current from the probe to the tissue. Such inert gas beam coagulators are available commercially from suppliers such as Con-Med and Valleylab.

Energy from the energy source is typically directed to the tissue using a probe connected to an external power supply. The treating physician usually directs the probe manually to apply energy over the surface of the matrix material and visually confirms that fusion has been achieved. Using an inert gas beam coagulator an energy output from about 2W to about 100W, preferably from about 20W to about 40W, will be used. The fusible material will typically be exposed to the energy for a total time from about 5 seconds to about 120 seconds, usually from about 10 seconds to about 40 seconds, for material having an area from about 1 cm² to about 10 cm². The precise timing will depend on the physician's visual assessment that the matrix material has fused to the underlying tissue.

Referring now to Fig. 1, an article 10 comprising a solid sheet 12 of matrix material comprising a non-collagenous protein component according to the present invention is illustrated. As shown, the sheet is square, but sheets having a variety of other regular and irregular geometries, such as rectangles, circles, ovals, and the like, could also be fabricated. The surface area, thickness, and other characteristics of the sheet 12 are preferably (but not necessarily) as described above.

The solid sheet 12 is usually packaged in a manner suitable to facilitate use by the treating physician. Generally, the sheet material is sterilized and packaged in a suitable container, such as a pouch, box, canister, bottle, or other conventional receptacle for medical products. In Fig. 2, the sheet 12 is illustrated as packaged in a pouch comprising a front sheet 14 and back sheet 16, where the sheets are laminated together around the edge to seal the interior of the package. Alternatively, the sheet material is rolled and packaged in order to provide larger areas of material. Sterilization of the sheet material 12 is accomplished, prior to, during, or after packaging. Suitable sterilization techniques include the use of sterilizing gases, sterilizing radiation, heat, or the like. Usually, the solid sheet 12 or other form of the material of the present invention will be packaged together with written instructions setting forth the methods described herein, i.e. that the materials are to be placed over a target site in tissue and energy applied to effect bonding. The instructions may be printed on the packaging material (e.g. on a box or on a pouch holding the material) or may be provided on a separate package insert which is placed in or on the product package.

Referring now to Figs. 3 and 4, the use of a strip 20 of the matrix material of the present invention for covering and sealing a wound W in a region of tissue T is illustrated. The strip 20, which has been be trimmed to size prior to use, is placed over the wound W as shown in Fig. 4. After placement of the strip 20, energy such as radio frequency energy is applied over the strip using a hand-held probe 22, as illustrated in Fig. 4. The energy is applied by passing the probe 22 over the upper, exposed surface of the strip to fuse the protein-containing strip to the underlying tissue. Exemplary power levels, exposure times, and the like, are described above.

Referring now to Figs. 5 and 6, an alternative method for applying matrix material to the wound W on the region of tissue T is illustrated. Liquid or gel matrix material 30 is applied using a syringe 32, typically in a

series of parallel strips 34. Other patterns of application, of course, could also be employed, such as circular, spiral, criss-crossed, and the like. It is generally desirable, however, that material be applied at a relatively uniform density over the tissue, so that, after application of energy, a generally continuous layer of matrix material 36 results, as shown in Fig. 6. Again, the energy is typically applied using the hand-held probe 22.

Referring now to Fig. 7, after the application of energy, the matrix material is in the form of a generally continuous layer 40 of material which adheres to the upper surface S of the tissue T. The layer 40 of material will adhere to the tissue T with a minimum peel bond strength as set forth above. Moreover, the layer 40 will have a relatively high tensile strength so that it can maintain the integrity of the tissue T over the wound W.

The following examples are offered by way of illustration, not by way of limitation.

EXPERIMENTAL

Summary

Patches were fabricated from bovine serum albumin, bovine fibrinogen, and bovine hemoglobin. Bonds were achieved with each of these patches, using an argon beam coagulator to deliver thermal energy. The tissue model was porcine or bovine lung *in vitro*.

Hemoglobin patches

Bovine hemoglobin (BHG, Sigma Chemical Co.) was dissolved in a buffer of 0.03M NaCl and 0.02M sodium phosphate, pH 6.8, to achieve a solution at 40 mg protein/ml. The protein was cross-linked by adding di-glycidyl PEG 600MW (DPEG, Polysciences, Inc.) and heating. One formulation was prepared by mixing 1.53 ml of BHG solution and 15.3 ul of a 10% (w/v) aqueous solution of DPEG in a polystyrene weighing boat (4.6 cm square), covered with aluminum foil, and heated at 50°C overnight. A second formulation was prepared in an aluminum sample pan and heated at 80°C in a water bath for

15 min. When dried, both films cracked into small shards approximately 5 mm in diameter. Shards could be bonded to an inflated porcine lung in vitro; the argon beam coagulator was operated at 40 watts of power, and 4 liters argon/min. The duration of the applied beam was approximately 15 sec per square centimeter of patch. Patches welded dry and after 5 min hydration in 0.9% aqueous saline exhibited bond strengths of approximately 0.03 Newtons/cm (peel test). Gelatin patches cross-linked with UV light under the same conditions exhibit peel strengths of 0.03 to 0.05 Newtons/cm. The hemoglobin patches remained intact during the peel test. Pliability and elongational deformation of hemoglobin patches were not evaluated.

15 Albumin patches

Bovine serum albumin (0.5g, Sigma Chemical Co.) was mixed in a polystyrene weighing boat 4.6 cm square with 1.5 ml 0.9% saline and held at 5°C overnight. At this point, the albumin had dissolved to yield a viscous solution. Glutaraldehyde (37% aqueous, w/v; 14 ul) was added and stirred rapidly into the albumin solution. Within minutes the albumin formed a continuous gel. It was dried under ambient conditions to a moist film. At this point, the partially dried film was dislodged from the polystyrene boat and wrapped in plastic sheeting to prevent further drying. For argon beam bonding to lung tissue, the moist film and a fully hydrated film (in 0.9% saline) were tested. Conditions for welding were as described above, except that the time for treatment of patches with the argon beam was approximately 5 sec per cm² of patch. The moist film yielded a bond strength (peel strength) of approximately 0.03 Newtons/cm; the fully hydrated film, approximately 0.01 Newtons/cm. Patches were removable as intact films (did not tear).

Albumin-polyacrylamide composite patches were prepared by mixing 167 mg bovine serum albumin, 1.67 ml saline, 0.62 ml stock acrylamide (30% aqueous acrylamide, 0.8% bis-acrylamide, w/v), 40 ul 10% (w/v) ammonium persulfate, and 8 ul TEMED (tetramethyl-ethylenediamine). The mixture was

poured into several polystyrene weigh boats (4.6 cm square) and allowed to polymerize at room temperature. Gels were allowed to dry at ambient to form moist mats and wrapped with plastic sheeting to prevent further drying. Moist mats were bonded by argon beam to porcine lung in vitro and yielded a peel strength of approximately 0.03 Newtons/cm; mats hydrated 5 min in saline did not bond after argon beam treatment. Mats were removable from the bond site in an intact state. Conditions for bonding with the argon beam were as for albumin patches as described above.

Fibrinogen patches

Bovine fibrinogen (Sigma Chemical co., 400 mg) was mixed with 9.6 ml of 0.3M NaCl, 0.02M sodium phosphate, pH 6.8, and held at 5°C for 16 hours to several days to permit dissolution of the fibrinogen (Dissolution was facilitated at the end by incubation at 37°C for 10 min). The solution was allowed to dry to a film with thickness of 0.04 to 0.05 mm. When bonded by the argon beam coagulator to porcine lung in vitro, the dry film yielded a bond peel strength of approximately 0.03 Newtons/cm and remained intact upon peeling. The hydrated film disintegrated and could not be welded. Conditions for bonding with the argon beam were the same as those used for albumin patches. Part of the dry film described above was cross-linked with 0.05% (w/v) glutaraldehyde for 3 hours. It was allowed to dry at ambient conditions to a damp mat. Upon bonding by the argon beam, a peel strength of approximately 0.02 Newtons/cm, and the film remained intact during peeling. The glutaraldehyde cross-linked preparation was repeated, and the dry peel strength was the same as above, the peel strength of a fully hydrated film was zero Newtons/cm.

Other fibrinogen films were prepared as described above and cross-linked with UV light (dose: 4200 mJ/cm² in a Spectrolinker XL 1500 UV cross-linking chamber, Spectronics Corporation, Westbury, NY). When bonded dry to the lung in vitro, a peel strength of approximately 0.03 Newtons/cm was observed; the film remained intact during peeling. The film

hydrated in saline remained intact, but curled into an irregular shape which was not suitable for a weld test.

5 Although the foregoing invention has been described in some detail by way of illustration and example, for purposes of clarity of understanding, it will be obvious that certain changes and modifications may be practiced within the scope of the appended claims.

WHAT IS CLAIMED IS:

1 1. A method for fusing a matrix material to
2 tissue, said method comprising:

3 providing a matrix material containing a non-
4 collagenous protein component which binds to tissue upon the
5 application of energy;

6 placing the matrix material over a target location
7 on the tissue; and

8 applying energy to the matrix material in an amount
9 sufficient to fuse the matrix material to the tissue.

1 2. A method as in claim 1, wherein applying energy
2 to the matrix material results in a layer of material which
3 fuses to the underlying tissue with a peel bond strength of at
4 least about 0.03 N/cm.

1 3. A method as in claim 1, wherein the layer has a
2 substantially continuous surface area of at least about
3 0.5 cm².

1 4. A method as in claim 1, wherein the layer has a
2 thickness of at least about 0.01 mm.

1 5. A method as in claim 1, wherein the non-
2 collagenous protein is selected from the group consisting of
3 albumins, hemoglobins, fibrinogens, fibronectins, elastins,
4 keratins, and laminins.

1 6. A method as in claim 1, wherein the matrix
2 material comprises the non-collagenous protein and a carrier
3 substance.

1 7. A method as in claim 6, wherein the carrier
2 substance is selected from the group consisting of collagen,
3 gelatin, fibrinogen, and elastin.

1 8. A method as in claim 1, wherein the matrix
2 material comprises a solid or mesh layer.

1 9. A method as in claim 1, wherein the matrix
2 material comprises a dispersible, non-solid phase selected
3 from the group consisting of liquids, gels, sols, suspensions,
4 and powders.

1 10. A method as in claim 1, wherein the matrix
2 material is placed over a wound at the target location in the
3 tissue to help close the wound.

1 11. A method as in claim 1, wherein the energy is
2 applied at a level in the range from about 1 W/cm² to about
3 100 W/cm² for a time sufficient to fuse the matrix material to
4 the tissue without a substantial loss of mechanical strength.

1 12. A method as in claim 1 wherein the energy
2 applying step comprises applying energy from the group
3 consisting of radio frequency energy, heat energy, laser
4 energy, microwave, infrared, and ultrasonic energy.

1 13. A method as in claim 12, wherein the energy is
2 radio frequency energy.

1 14. A method as in claim 13, wherein the energy
2 applying step comprises directing energy from a radio
3 frequency inert gas coagulator applicator against the matrix
4 material at the target location.

1 15. An improved method of the type wherein a matrix
2 material is fused to tissue upon the application of energy,
3 wherein the improvement comprises providing a matrix material
4 including a non-collagenous protein component which binds to
5 tissue upon the application of energy.

1 16. An improved method as in claim 15, wherein the
2 non-collagenous protein is selected from the group consisting
3 of albumins, hemoglobins, fibrinogens, fibronectins, elastins,
4 keratins, and laminins.

1 17. An improved method as in claim 15, wherein the
2 matrix material comprises the non-collagenous protein and a
3 carrier substance.

1 18. An improved method as in claim 17, wherein the
2 carrier substance is selected from the group consisting of
3 collagen and gelatin.

1 19. An improved method as in claim 15, wherein the
2 matrix material comprises a solid or mesh layer.

1 20. An improved method as in claim 15, wherein the
2 matrix material comprises a dispersible, non-solid phase
3 selected from the group consisting of liquids, gels, sols,
4 suspensions, and powders.

1 21. A tissue closure matrix material comprising a
2 non-collagenous protein component which fuses to tissue upon
3 the application of energy.

1 22. The material as in claim 21, which binds to the
2 underlying tissue with a peel bond strength of at least about
3 0.03 N/cm.

1 23. The material as in claim 21, wherein the sheet
2 has a substantially continuous surface area of at least about
3 0.5 cm².

1 24. The material as in claim 21, wherein the sheet
2 has a thickness of at least about 0.01 mm.

1 25. The material as in claim 21, wherein the non-
2 collagenous protein is selected from the group consisting of
3 albumins, hemoglobins, fibrinogens, fibronectins, elastins,
4 keratins, and laminins.

1 26. The material as in claim 21, wherein the matrix
2 material comprises the non-collagenous protein and a carrier
3 substance.

1 27. The material as in claim 26, wherein the
2 carrier substance is selected from the group consisting of
3 collagen and gelatin.

1 28. A package containing the material of claim 21,
2 wherein the package is sealed and the article is sterilized
3 therein.

1 29. The package of claim 28, further comprising
2 written instructions to place the material over tissue and to
3 apply energy to the material and tissue to bond the material
4 to the tissue.

1 30. The material as in claim 21, wherein the matrix
2 material comprises a solid or mesh layer.

1 31. The material as in claim 21, wherein the matrix
2 material comprises a dispersible, non-solid phase selected
3 from the group consisting of liquids, gels, sols, suspensions,
4 and powders.

1 32. The material as in claim 21, wherein the non-
2 collagenous protein component binds with the application of
3 energy at a level in the range from about 1 W/cm² to about
4 100 W/cm² for a time selected to fuse the matrix material to
5 the tissue.

1 33. The material as in claim 32, wherein the energy
2 is from a radio frequency inert gas device.

1 34. An article comprising:
2 a film of a tissue closure material comprising a
3 non-collagenous protein;
4 a sealed package holding the film, wherein the film
5 is sterilized therein; and
6 written instructions to place the film over tissue
7 and to apply energy to the tissue to bond the material to the
8 tissue.

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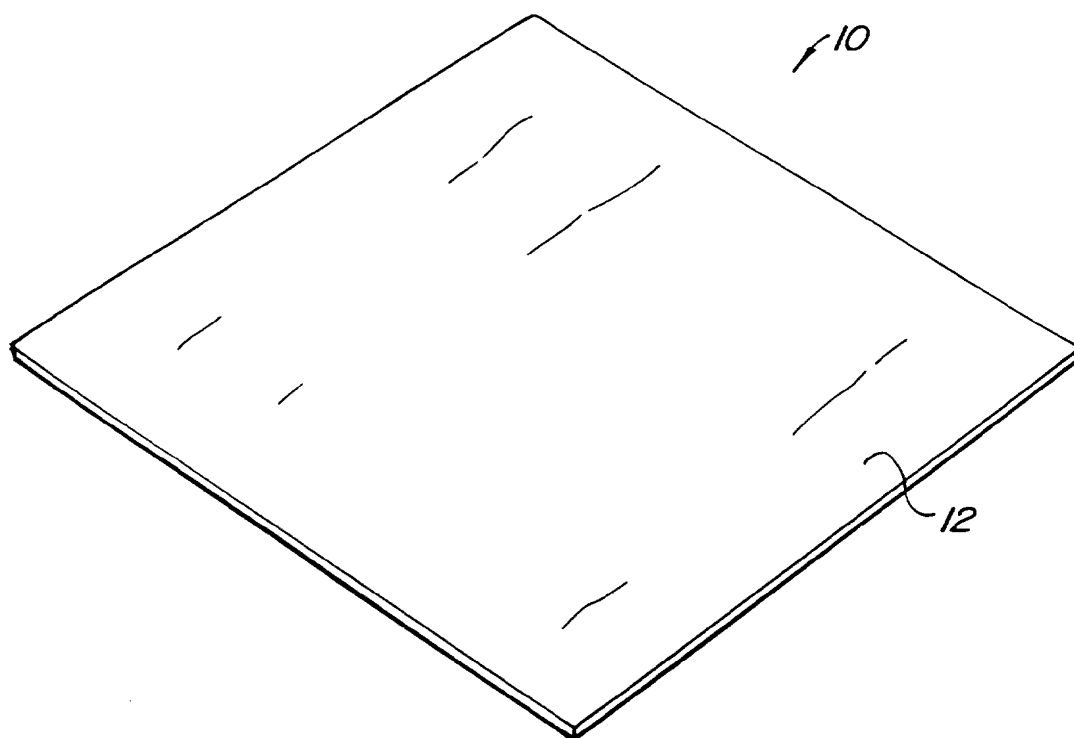


FIG. 1.

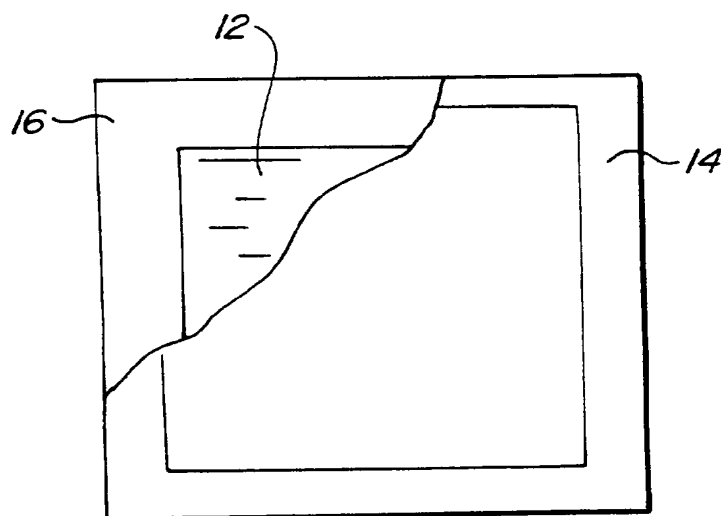
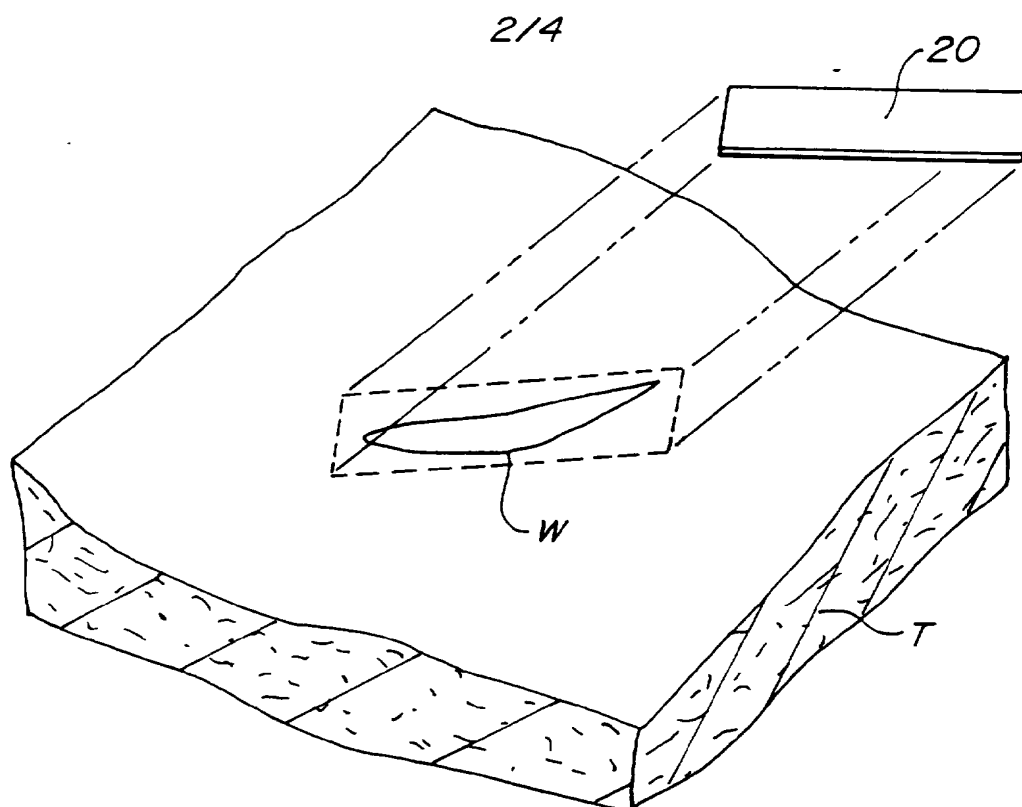
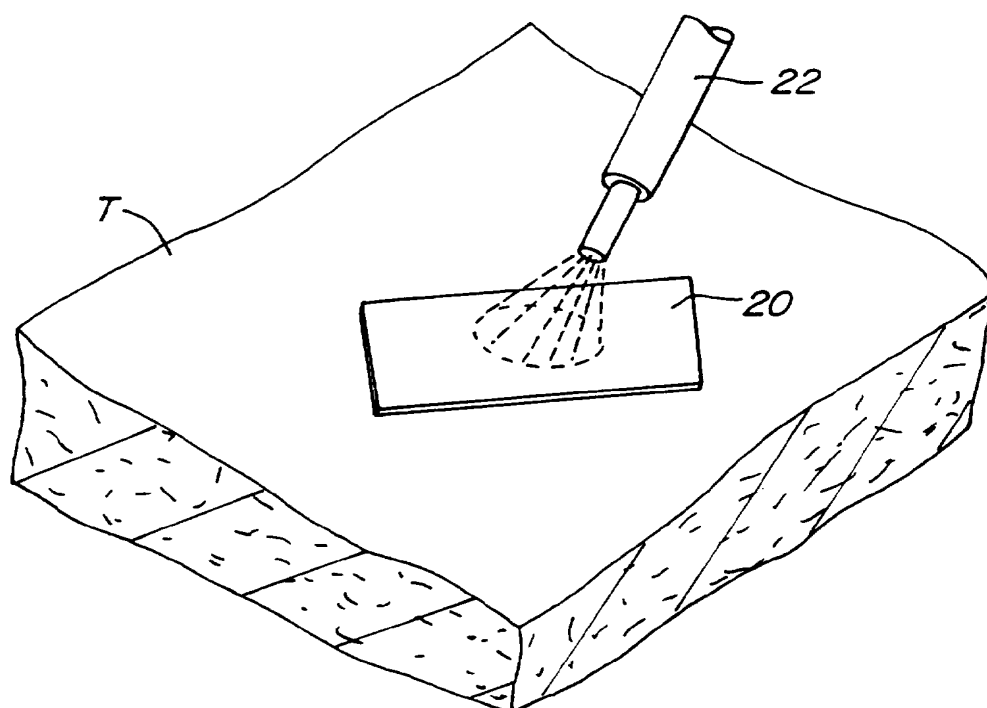
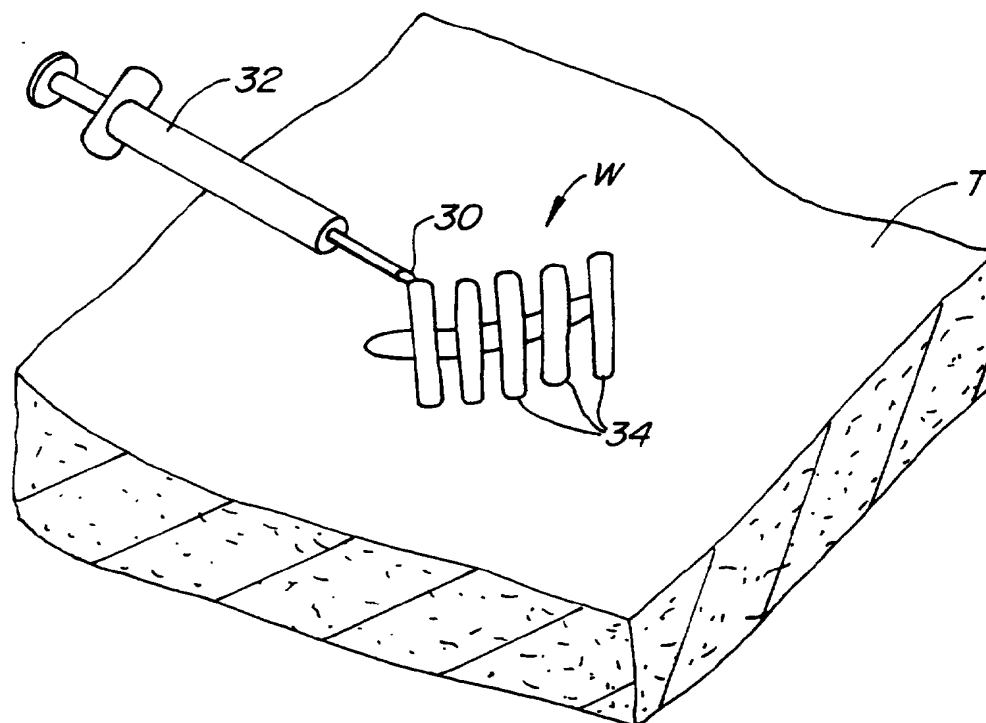
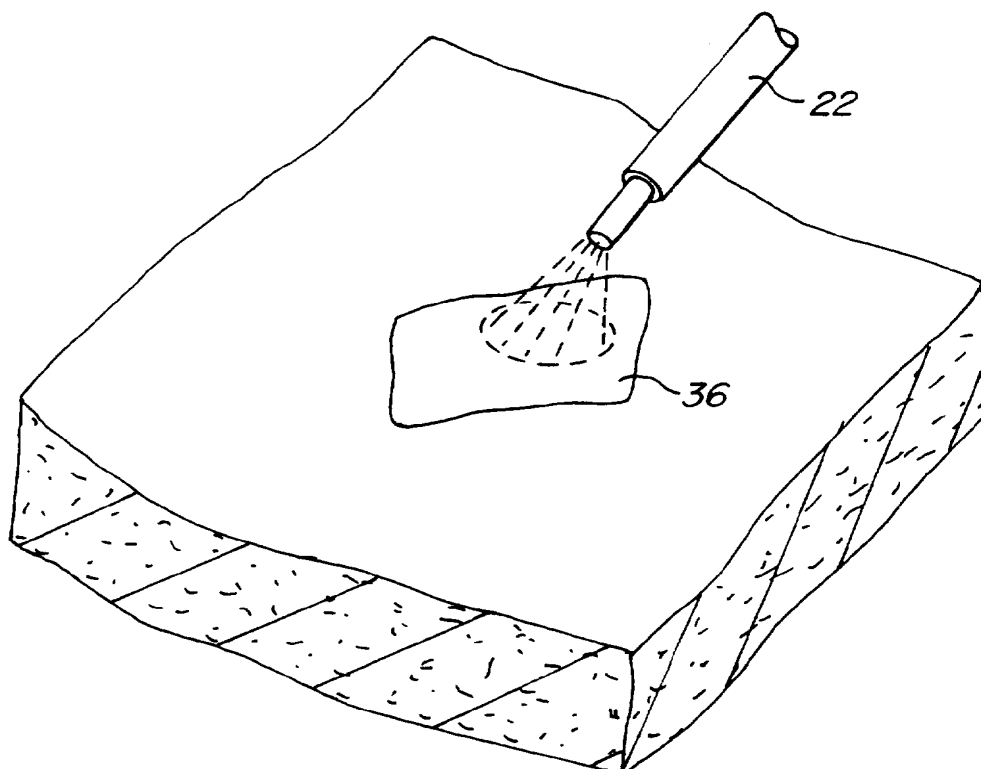


FIG. 2.

**FIG. 3.****FIG. 4.**
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**FIG. 5.****FIG. 6.**
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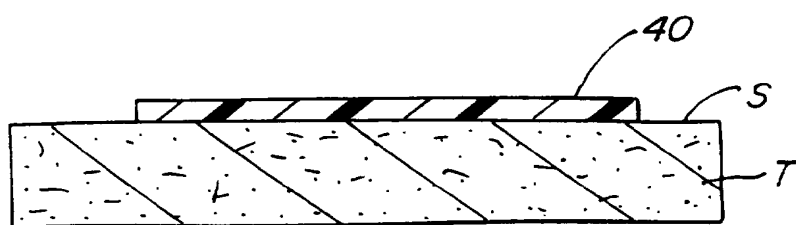


FIG. 7.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US96/17854

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61B 17/08

US CL : 606/213, 214

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 606/213, 214

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,209,776 A (BASS et al) 11 May 1993, col. 4, lines 1-3, 33-38, 40, 58-61; col. 5, lines 2-17; and col. 7, lines 28-46.	1, 5-10, 12, 15-21, 25-27, 30, 31 ----- 11, 13, 28, 32, 33
Y	US 5,156,613 A (SAWYER) 20 October 1992, col. 2, lines 56-65; col. 3, lines 37-49; and col. 4, lines 1-4.	13, 33
Y	US 3,527,224 A (RABINOWITZ) 08 September 1970, col. 2, lines 56-61.	28



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

30 DECEMBER 1996

Date of mailing of the international search report

21 JAN 1997

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